Fostering Communication and Collaboration

The NIH Catalyst

A Publication for NIH Intramural Scientists

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New Standards Set For NIH-Based Clinical Research

About six years ago, when the Clinical Center was devising a course on the principles and practice of clinical research, CC Director John Gallin contemplated the complementary creation of *standards* for clinical research at NIH—a blueprint to facilitate a transition from the armchair to the frontlines of clinical research on campus.

Other institute directors wanted standards, too, and some clinical directors readily expressed frustration over gaps in the clinical research infrastructure at their institute that could be corrected by uniform standards.

But the timing wasn't right then, Gallin recalls. Other changes to support clinical research were under way, and clinical standards, per se, were put off.

The timing was right, though, in January 1999, when a presentation before the CC Board of Governors detailed the variability among institutes in resources—appropriate staff, biostatistical expertise, protocol review mechanisms, monitoring capabilities, and data collection—to support the conduct of intramural clinical research.

The Board recognized a need for trans-NIH standards, which led the CC Medical Executive Committee (MEC) to hold a retreat last March. Standards were drafted, massaged, and reviewed by the CC Advisory Council and the scientific directors;

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Elaine Jaffe: Hercule Poirot In a Pathological Universe

by Cynthia Delgado

One of the world's most called-upon resources in the field of hematopathology resides in NCI's Laboratory of Pathology, where she serves as deputy chief and from where she responds to distant calls for help, unravelling the diagnostic dilemmas sent to her by clinicians the world over and by patients seeking impartial advice on treatment options.

Cynthia Delgado

Elaine Jaffe at her window on the world of disease

Last year, the Institute for Scientific Information released survey results, reported in the May-June 1999 issue of *Science Watch*, that named Elaine Jaffe among the 100 most-cited researchers in clinical medicine and among the top 10 in oncology between the years 1981 and 1998. She was the only female clinician listed, which she sees predominantly as a reflection of the realities of the years covered in the survey. "Back in 1981," she says, "there were fewer women in the field and fewer women publishing. I would hope that if we did a survey from, let's say '90–'98, there would be many more women included." Asked if being a woman in science had presented any particular challenges to her research, she replies, "Not really." And asked to what she attributes her success, she credits the "unique scientific environment of NCI."

In an interview with *The NIH Catalyst*, Jaffe elaborated on the advances in immunology and molecular genetics that have transformed the tools of pathologic diagnosis and the classification systems for lymphomas and leukemias and, with unfolding microarray technology, the molecular disease profile of all cancers. She emphasized the clinical context of pathological findings, without which the disease entity may fail to be appreciated and optimal management may remain elusive. And she sang the praises of the contributions and rewards of her profession. Far from being "locked in a morgue," as the public may perceive them, pathologists perform exquisite detective work that uncovers disease mysteries and helps keep people alive and healthy.

The interview follows.

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Giving a Scintillating Scientific Talk

Michael Gottesman

In this space, I frequently hold forth about the importance of attending lectures at NIH to keep abreast of current developments in a field and to broaden one's scientific perspective.

The Wednesday Afternoon Lectures and the Friday noon NIH Director's Seminar Series were developed to expose a general audience—NIH trainees and scientists—to the best and most interesting aspects of current biomedical research.

Most of these lectures live up to our expectations, but more than occasionally, a speaker has difficulty explaining the importance of his or her work or fails to convey the most basic concepts underlying the research.

A recent complaint from an NIH scientist about the obscure nature of some of our lectures (see "Catalytic Reactions," page 3) prompted this essay on clarity in speaking about science.

Principle #1:
You should never assume that a general audience knows the nature of the biological phenomenon or question that has captivated you. You cannot even assume the audience has any special interest in the problem at hand.

So in the first few minutes of the talk, or in the first few slides, explain in simple terms the issue of interest and why you found it so engaging and important. For example, there might be some clinical relevance worth mentioning, or perhaps an important underlying biological principle is at stake.

The intent of your introduction should be to intrigue the audience and discourage them from falling asleep before you've even gotten to the data.

Principle #2:
Make sure a logical thread flows throughout your narrative. The best talks tell a story. The story may unfold historically or sequentially; it may weave together what at first appear to be diverse facts or fields; or it may be a who-done-it or how-we-done-it showing how you solved a long-standing mystery or problem presented in the introduction.

Merely pulling out a series of disconnected slides and showing them is bound to result in audience confusion.

Principle #3:
The story line of your talk can never be too simple. Even the brightest people appreciate clear explanations and rationales.

On the other hand, you should not insult an audience by leaving out complex experiments that are important to your argument. Omitting these from a talk leaves a logical gap that the intelligent listener cannot fill. By all means, discuss the complex experiments—but describe them in the simplest possible terms.

YOU SHOULD NEVER ASSUME THAT A GENERAL AUDIENCE KNOWS THE NATURE OF THE BIOLOGICAL PHENOMENON OR QUESTION THAT HAS CAPTIVATED YOU. YOU CANNOT EVEN ASSUME THE AUDIENCE HAS ANY SPECIAL INTEREST IN THE PROBLEM AT HAND.

Principle #4:
Visual aids in your presentation—usually slides, overheads, or movies—should be relevant to the talk and free of extraneous information.

When a slide comes up, the audience begins to scan it, and the talk that accompanies each slide should aid the audience in understanding the data or pictures on the slide.

All too often, slides are cluttered with complex, extraneous information that confounds rather than enlightens the listener.

Clear slides are especially important if you are not a native speaker of your audience's language. The principle that "simple is better" holds for slides also.

Principle #5:
Finally, assume the audience will not absorb everything you say during the talk. Do not be afraid to repeat a conclusion or important point during a talk. And always have a set of conclusions that the audience can take home.

In keeping with the final principle, here's my take-home lesson: Think of yourself as a member of the audience who has not had a lifetime of experience working on your subject and speak to that person.

—Michael Gottesman
Deputy Director for Intramural Research

Just Ask!

Dear Just Ask:

A Chinese graduate student would like to do his thesis research in my lab for a Ph.D. from his university in China. Can I bring him here on a J-1 visa as a research associate at a salary appropriate for a graduate student? If not, how do we do it?

—Edward Korn, NHLBI

Dear Ed:

We have a program—the Predoctoral Visiting Fellow Program—established specifically for the purpose you mention. It's a predoctoral training program for students enrolled in doctoral programs in non-U.S. universities and is a collaborative effort between NIH and the Molecular and Cell Biology Program (MOCB) at the University of Maryland in College Park. The student comes to the United States on an F-1 Student Visa sponsored by the university, and NIH pays the university to run the program for us.

Students are registered for at least one year at the university as Advanced Special Students while they are participating in research in NIH laboratories; NIH scientists serve also as teachers, advisors, and mentors.

To be eligible for the program, students must be enrolled in a doctoral training program in the biomedical sciences. To apply, a student submits a letter of intent to the MOCB Program, as well as a formal application to the Graduate School for admission as an Advanced Special Student. Items that must be submitted with the application include:

- At least two letters of recommendation from professional or academic references.
- An official graduate school transcript.
- A statement of professional goals, areas of research interests, and the objectives to be accomplished during the training.
- A report of the score obtained by the applicant on the Test of English as Foreign Language (TOEFL) examination.

Selection is competitive and based on evaluations by staff at both the University of Maryland and NIH. Those accepted into the program will receive a stipend and are eligible for health benefits and a tuition remission.

Fran Pollner

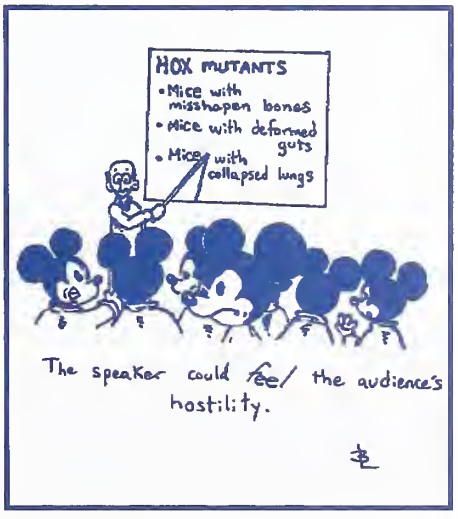
Philip Chen

Application materials should be submitted by:

- February 1, for admission in the summer semester.
- May 1, for admission in the fall semester.
- November 1, for admission in the spring semester.

For additional information, contact the MOCB Program, Microbiology Building, Room 1123, University of Maryland, College Park, MD 20742, U.S.A.; phone: (301) 405-8422; fax: (301) 314-9921; e-mail: <**LP101@umail.umd.edu**>. You can also check the web site at <**http://www.life.umd.edu/grad/mocb/mcb-nih/**>.

—Philip S. Chen, Jr.
Senior Advisor to the Deputy Director for Intramural Research



Catalytic Reactions

On Lectures at NIH

In the November-December 1998 issue of *The NIH Catalyst*, Michael Gottesman encouraged us to "make space" in our schedules for activities that broaden our scientific horizons. He specifically recommended attending lectures. However, in trying to implement his excellent suggestion, I am disheartened by the overcomplexity of many—perhaps most—lectures I attend.

I find it extremely frustrating to spend an hour or so of my valuable time only to find slides that are overly complex or a presentation that seems geared to the handful of people who are as up on the literature of that subject as the speaker! Perhaps I am too specialized. I could prepare by reading pertinent literature—but I don't have time for that! Shouldn't the hour I spend in the seminar be enough to learn the background, the research, and its implications? Perhaps I have an attention problem. But our minds drift naturally in even more dramatic presentations than a typical scientific talk. Some speakers seem more concerned with showing people how much work they've been doing than in presenting a clear message that is understood by a general scientific audience! I want to scream in agony whenever I hear a speaker "apologize" for a complex slide or go over time just to squeeze in some more data! The end result for me is that I don't attend as many lectures as I would like. Hence, I don't learn as much as I would like.

Can anything be done about these overspecialized lectures? As a listener, how can I get the most out of a presentation? As a speaker, what should I do to give a good talk? I think it would be a good investment of our time to "make space" for improving lectures we give and attend.

—David Belnap, NIAMS

—See the DDIR's response "Giving a Scintillating Scientific Talk," page 2.

Write Right. Ya Gotta.

by Celia Hooper

No sooner do we get by Y2K and along comes another challenge. Ready or not, it's time to grapple with Vice President Al Gore's Plain Language Initiative. According to the June 1, 1998, Presidential Memorandum on Plain Language, all government agencies must use plain language in new customer service documents as of October 1, 1998. By January 1, 1999, all the rules published in the Federal Register should be written in plain language. And by January 1, 2002, every piece of writing that explains "how to obtain a benefit or service or how to comply with a requirement you administer or enforce" must be in plain language.

Karen O'Steen, who heads the Executive Secretariat (ES) in the Office of the Director, will be heading NIH's Plain Language efforts. O'Steen says the initiative will be good for NIH. "Plain language is a requirement that makes sense. The ultimate goal of NIH research," she observes, "is to improve people's health, and that won't happen unless we communicate clearly our research results to our "customers" — the public, our grantees, physicians, the Congress, and others."

Ruth Kirschstein, NIH acting director, sees the initiative as a bread-and-butter issue. "Surveys have shown that the American people support biomedical research—even when they do not know what it is. It is the responsibility of all of us at NIH to explain what we do and why it is important in 'plain language' so that we continue to have the trust and support, through taxpayers' dollars, to add knowledge that will improve the health of the public."

What has to be written in plain language at NIH?

NIH doesn't do much administering or enforcing of requirements, but that doesn't get us off the hook. Thinking of writings generated by NIH research and the kinds of things I myself write or receive from colleagues at NIH, numerous examples presented themselves to me, such as:

- Fact sheets
- Patient consent documents
- Web pages
- Letters to potential trainees
- Requests and instructions for extramural grant proposals
- Responses to colleagues requesting a cell line

If you consider that other NIH staff are the "customers" for administrative memos, the writing we do for other NIHers could probably benefit from plain language handling, including:

- Memos on how to use a purchase card
- The charge to a committee
- Directions to the lab picnic

Arguably, even research descriptions in annual reports—although they are aimed at a technical audience—could benefit from plain language principles. These reports communicate the knowledge NIH has gleaned with taxpayer dollars and, as President Bill Clinton's directive says, "By using plain language, we send a clear message about what the Government is doing."

Why should I use plain language?

It *is* required for all executive-branch agencies, but there are plenty of other good reasons to use plain language, say the experts in the ES, who are charged with getting NIH to write right. Dale Johnson, ES deputy director, told the first meeting of NIH's Plain Language Coordinating Committee (PLCC) that plain language:

- Gets the message across quicker and better
- Increases reader understanding and compliance
- Cuts staff writing, editing, and rewriting work
- Saves time and money

Nancy Miller, the plain language guru for OD's Office of Science Policy, says plain language can even improve public health. She cites an August 18, 1999, article in *JAMA* that shows that an easy-to-understand brochure increased the rate of pneumococcal vaccination.

Alison Wichman of the Office of Human Subjects Research is developing an online tutorial for writing clear patient consent documents. Wichman points to research showing that patients at all educational levels understand consent forms better if they are written in plain language (D.R. Young, D.T. Hooker, and F.E. Freeberg. "Informed Consent Documents: Increasing Comprehension by Reducing Reading Level," *IRB Rev Hum Subj Res* **12**(3):1–5, 1990).

Jon Holmes, a contractor who teaches bureaucrats how to use plain language, says the advent of electronic communications has increased the importance of efficient writing. He says studies show that reader speed and comprehension of e-mail is about half that for print documents. Unfortunately, the average time a reader will devote to understanding an electronic document is shorter, not longer.

How do I write in plain language?

Strategy: The key to plain writing is identifying with the audience, says Johnson. Holmes' course emphasizes "reader-centered writing." Patrick Boyd, a senior regulatory analyst at the Bureau of Land Management (BLM) who volunteered to teach the PLCC how to use plain language, says the focus should be on what the reader needs to know, rather than what the writer wants to say.

Taking a reader-centered approach means crafting documents that are concise, to the point, unambiguous, and organized so that readers can quickly find what they want to know. Clinton's memo says that plain language documents have logical organization, easy to read design features, and use:

- Common, everyday words, except for necessary technical terms
- "You" and other pronouns
- The active voice
- Short sentences

Holmes recommends taking a few minutes before you start writing to analyze your audience and define the purpose of the document. Key questions include:

- What should the reader get from this?
- Who is my reader?

The answers to these questions should dictate what you say and how you say it.

Organization: Boyd uses a BLM document, written before the days of plain language, to demonstrate that good writing starts with good organization. Although the point of the BLM brochure is ostensibly to tell citizens how to appeal BLM actions, the table of contents yields no clue where to begin. A better approach is to identify the key information potential readers will seek from a document and organize it around those points, usually starting with the most important point. Holmes calls this "putting the bottom line on top."

To focus on what the reader needs to know, Boyd often recommends question-and-answer format for documents. Within the document, bulleted lists and brief, informative headlines and subheads help readers locate information more quickly. In his spiel to the PLCC,

Boyd showed that tables can give readers massive amounts of detail quickly, sometimes sparing them many paragraphs of dense prose.

Other tricks that enhance the visibility of information also improve readability. These include using:

- Double columns
- Informative headings
- Margin notes
- Short paragraphs
- **Boldface** and *Italics* to emphasize key concepts
- Lists
- Indenting
- Charts

In general, shorter is better—shorter words, sentences, paragraphs (aim for four to six lines, with just one topic per paragraph), and documents. But Boyd does not recommend getting rid of all the white space in a document to shorten it. Space around and between the sections of a document actually makes it more readable, he says.

Clear Sentences: The basic building block of plain writing is the clear sentence. In addition to keeping sentences short—an average of 15 to 20 words is good—you should strive for clarity, says Johnson. "Write not just to be understood, but to avoid misunderstanding," she advises.

In addition, plain sentences:

- Use short, familiar words wherever possible
- Are streamlined with no extra words
- Have active rather than passive construction (see box)
- Feature strong, specific verbs and the simplest verb tense possible
- Are varied in structure and length
- Avoid negative constructions (see box)
- Refer to the reader as "you" and the writer or agency as "we"

Where can I get help?

Help abounds. On the Internet, the National Partnership for Reinventing Government's "Plain Language Action Network" is an excellent aid:

<http://www.plainlanguage.gov/>

The site includes links to Canada's Plain Train—online plain language training—and other resources.

NIH's local plain language initiative has established a website that includes the presidential and NIH Plain Language memos:

<http://www1.od.nih.gov/execsec/plainlanguage.htm>

The NIH Training Center offers plain language training:

<http://trainingcenter.od.nih.gov/>

(see Communications Skills)

Some training is available through the USDA and various contractors. Your IC's PLCC member or the ES office may be able to refer you to these and other trainers. Some institutes may arrange and require plain language classes for their staff.

What's the plain language plan for NIH?

NIH is taking a velvet-gloved approach to implementing the Plain Language Initiative. "We know that if we tried to force this down people's throats at NIH, it wouldn't work," O'Steen says. After assembling the PLCC, O'Steen divided the large group into three committees: Training, Media, and Evaluation and Awards. Now it is up to PLCC members to use the bully pulpit and some centralized efforts by the three committees to induce, cajole, or harangue NIHers to write right.

One inducement O'Steen and the Evaluation committee are planning is awards for Plain Language achievements. ES's Geri Lipov says her office wants NIHers to send them good examples of plain language communications. Lipov especially wants "Before and After" examples showing how a document was improved through plain language. Her office will consider submissions for Gore's "No Gobbledygook" awards as well as NIH awards.

PLCC members—some clearly passionate about good writing—are divided on how tough it will be to get NIH writing plainly. At a recent meeting of the PLCC, Katherine Kaplan, plain language representative for NCRR was optimistic: "What we're asking people to do is just write a good sentence. What's the big deal?" NHLBI's Nancy Eng was less certain. "It's not that easy. Not everyone is a born writer."

O'Steen says she agrees with William Zinnser, author of "On Writing Well," who acknowledges that good, clear writing is one of the most difficult things a person can do. But she is confident that NIH will rise to the task. "As a result of this initiative, I expect NIH's communications—in the broadest sense of that term—to be as outstanding as our biomedical research." ■

Quick Tips To Put It Plainly

■ **Gear your writing to the audience**: Aim for junior high school level for public information; higher reading levels are okay for technical documents. You can quickly get a crude estimate of the grade level of your writing by using the scales built into popular word-processing programs. (In Word, select text to be rated, then "Grammar" from the "Tools" menu. You must first have checked "Show Readability Statistics" under "Tools Preferences." For WordPerfect, look in "Grammatik.") *Example*: The grade level of the writing in this article is about 9.

■ **Use the active voice:** Active sentences are clearer, more precise, and engage the reader. Make sentences active by starting with the subject that performs the action of the verb. Use "we." *Example*: Active: "We modified the technique…" Passive: "The technique was modified…"

■ **Keep it short and simple:** Common, everyday words and shorter sentences are more understandable. Where possible, and especially in public documents, avoid jargon. Sentences should average 15 to 20 words.

■ **Use personal pronouns:** "You" and other pronouns engage readers. *Examples*: "You may apply on the web." "I will send the cells to you."

■ **Pick positives:** Negatives can confound meaning. *Example*: Positive: "The result had consequences." Negative: "The result was not inconsequential." ■

Use	Instead of
So	Accordingly
Allow	Afford an opportunity to
To	In order to
Use	Utilize
And, depending on the context, scientific terminology can *sometimes* be simplified	
Iron deficiency anemia	Hypochromic microcytic anemia
Cancer	Neoplasia
Heart attack	Myocardial infarction

NIH's Hercule Poirot
continued from page 1

Q: What lured you into the study of pathology?

JAFFE: During medical school, I came to realize I was *very* interested in the process and the pathogenesis of disease and less interested in dealing with patients on a one-on-one basis. It was the pathology course I took as a second-year medical student that was pivotal; it was then that I saw pathology as laying the groundwork for the understanding of all disease states—that the morphologic aspects of a disease often provide clues to its pathogenesis. It's a visual approach. I think pathologists do tend to be very visual in their outlook.

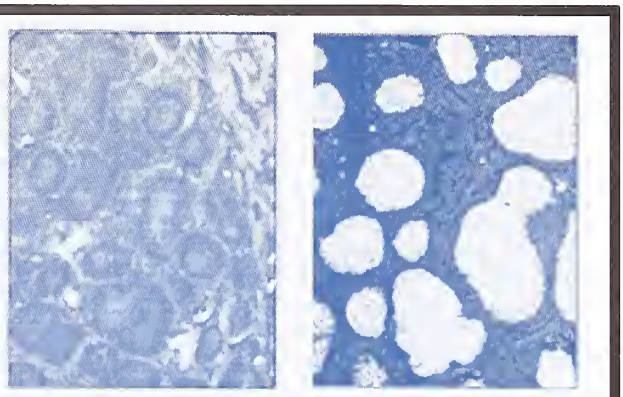
Q: How did you get to NIH?

JAFFE: While I was doing a pathology internship at Georgetown University (in Washington, D.C.), I learned that NIH had a residency in pathology—a not-well-publicized residency; it wasn't until moving to the area that I learned of it.

Q: What was going on in the field then?

JAFFE: I came here in 1970, and it was a time of explosive changes in the treatment of cancer at the NCI. Chemotherapy was really coming into its day and was expected to change the prognosis in many forms of cancer—in particular lymphoma, which has often been a model for treating other malignancies.

Vince DeVita and [his colleagues] were treating patients with Hodgkin's disease and non-Hodgkin's lymphoma. The residents had extensive exposure to hematopathology cases, and there was excitement about the clinical trials taking place. The field of immunology was also undergoing explosive growth. People were starting to dissect out the differences between T-cells and B-cells and developing tools to identify them in the laboratory and ultimately in tissue specimens. I decided to continue my training in the field by doing a fellowship here in hematopathology with Costan Berard, who was head of hematopathology at the time. He was an excellent diagnostic hematopathologist; [to strengthen our immunology base] we set up a collaboration with NIAID scientists to adapt some of the techniques that had been used in murine systems in order to identify lymphocytes in human disease. This was before the era of monoclonal antibodies, and the techniques we used—E-rosette and EAC-rosette—would be considered very primitive by today's standards.



From: E. S. Jaffe, E. M. Shevach, M. Frank, C. W. Berard, I. Green. *NEJM* 290:813-819, 1974.

A Page from History: *Clustering of tumor cells by then-new antibodies (right) vastly improved diagnosis of follicular lymphoma*

Q: Could you give us a brief history of the classification system for lymphomas and how we derived the current system?

JAFFE: Historically, classification schemes by pathologists had been primarily morphologic using H&E [hematoxylin and eosin stains]. An H&E slide can give you very limited information about the disease identity. In the 1970s, people began to apply immunologic tools and concepts to the study of lymphomas—but those techniques could not be widely used, and there was a lot of controversy over lymphoma classification, with half a dozen different classification schemes being used. In 1982, the Working Formulation (WF) was published. This classification scheme was used in the U.S. until 1994, when the REAL [Revised European-American Classification of Lymphoid Neoplasms] classification was published. The WF was a purely H&E approach, proposed at a time it was thought it would not be technically feasible for pathologists to recognize T-cells and B-cells as part of daily work. Such designations were considered applicable for research only. The major drawback of the WF was that it didn't identify disease entities. The heterogeneous categories didn't allow pathologists and clinicians to study individual diseases in terms of their biology, natural history, or response to therapy.

Q: What advances enabled progression from the WF to the REAL?

JAFFE: Monoclonal antibody technology was developed, which permitted the generation of a huge battery of reagents that could be produced with great specificity and great consistency and from laboratory to laboratory. While the first antibodies could only be used on frozen sections, subsequent antibodies were developed that could be used on routine paraffin sections. This meant the technology could really be exported to every pathologist, whether at a major medical center or a community hospital. Also, these antibodies could be used in immunoperoxidase techniques, which allowed a permanent record.

Q: You've written that "The REAL classification stressed the distinction between a disease entity and a prognostic factor." What are the most important features of REAL?

JAFFE: I think the important aspect of REAL is in identifying lymphomas as individual disease entities using morphologic, immunophenotypic, and molecular tools while integrating clinical features into the definition of disease entity. For instance, in another classification system that was used extensively in Europe, what was developed for nodal lymphomas was extrapolated to extranodal lymphomas. It was assumed that a lymphoma in a lymph node and a lymphoma in the GI tract were the same. The REAL system recognized that the presentation of lymphoma in a particular anatomic site was a clue to its biology.

Q: How was REAL initiated?

JAFFE: In 1990, several European scientists decided to initiate a working group of pathologists interested in the study of lymphomas. There were 17

hematopathologists at the first meeting in London. One of the topics of discussion was mantle cell lymphoma (MCL), which at that time was not recognized as a disease entity in the WF. At NCI, it had been described as "lymphocytic lymphoma of intermediate differentiation," meaning intermediate between poorly and well differentiated. In Europe, a similar process had been called "centrocytic lymphoma." In the 1970s, we had first suggested that this lymphoma might be related to the follicular lymphoid cuff or mantle, based on morphologic and enzymatic properties. Prior to monoclonal antibodies, hematopathologists relied on the expression of certain enzymes as another way to characterize cells. We had identified alkaline phosphatase expression on the cells we called "intermediate lymphoma." Subsequently, both at NCI and in other laboratories, translocations involving the *bcl*-1 breakpoint region and the immunoglobulin genes were seen in these lymphomas. At the London meeting, a consensus emerged that this lymphoma was derived from mantle cells, had a characteristic immunophenotype, and had consistent genetic abnormalities. The group, now named the International Lymphoma Study Group, published a consensus paper in 1992 proposing that MCL be recognized as a distinct disease entity. Importantly, this is not just a semantic issue. The ultimate definition of MCL is not equivalent to either "intermediate lymphoma" or "centrocytic lymphoma." Biological studies have been crucial in defining the borderlines of disease entities. With this success behind us, the group started to meet every year.

Q: A progress report, of which you are first author, was recently published in the *American Journal of Clinical Pathology*, describing the proposed World Health Organization (WHO) classification for lymphomas. What's the relationship between the REAL and WHO classification systems?

JAFFE: The World Health Organization publishes consensus handbooks on classification systems for all the neoplastic diseases. They hadn't published such a classification for hematopoietic or lymphoid diseases since the 1970s. About five years ago the coordinator of the WHO classifications approached the Society for Hematopathology, of which I was then president, to help develop a new classification scheme for the WHO. Not wanting a unilateral point of view, we approached the European Association of Hematopathology to work on this with us. First, the REAL classification had been validated in clinical studies and could serve as a template for the classification of lymphomas for WHO. Second, the priniciples of the REAL could be applied to other hematopoietic malignancies. In particular, the classification of acute leukemia had not changed in 20 years and was based on an outdated scheme that did not include immunologic or genetic concepts. Just as things had changed in lymphomas, they had also changed in leukemias, with the recognition of consistent cytogenetic abnormalities in many types of leukemias that correlated with prognosis and response to therapy. The concepts of disease definition within the REAL classification were thus applied to the leukemias, to histiocytic neoplasms, and to all diseases of the hematopoietic and lymphoid systems.

Q: Just how far could we extend the principles established by the REAL classification system? Could we expect that at some point in the future, our ability to diagnose disease will become as easy as accessing a computerized spreadsheet of characteristics—your basic profile of disease?

JAFFE: Yes. I think these concepts should be applied across the board to all cancers. I think microarray technology is trying to do that and that microarrays may be the monoclonal antibodies of the future. Monoclonal antibodies are advantageous because they are broadly applicable, can be used on a large scale reproducibly, and can be applied by scientists in many different laboratories. Microarrays have the potential to take the molecular expression of a neoplasm to the next level and to produce a consistent molecular profile.

Q: Are you currently using microarray technology in your research?

JAFFE: We've had some collaborations with Lou Staudt [Metabolism Branch, NCI] and plan future collaborations with him in terms of applying his microarray technology of the lymphochip to the study of lymphomas. And Mark Raffeld in our group has used other types of gene expression arrays to look at lymphomas on a smaller scale.

Actually, the genetic profile of only a small number of lymphomas is very well characterized, including follicular lym-

Vita

Cynthia Delgado

Elaine Jaffe came to NIH in 1970 and within a decade had established the reputation that mandated her presence anytime and anywhere the scientific community set about to resolve difficult issues in hematopathology. She was instrumental in the development of REAL, a classification system for identifying lymphomas adopted in 1994 and currently considered the gold standard. Her vita contains more than 400 published works (with another 13 currently pending) that have helped shape the theory and practice of her field.

Her honors, awards, seats on editorial and advisory boards, society memberships, fellowships, and educational activities are—as is often said when a supremely distinguished individual is introduced at a gathering—too numerous to be listed. At NIH, she lectures to summer students and mentors hematopathology fellows.

Her advice to young scientists reflects her own personal style: "Focus on a problem and finish what you start. Be committed and enjoy what you are doing. If you enjoy what you are doing, then you're excited about it, and you'll be successful."

—Cynthia Delgado

phoma and mantle cell lymphoma. There are a lot of other diseases that are not as well characterized. But as the human genome is further characterized and we use microarrays and develop more tools, we will uncover the precise genetic abnormalities for most of the lymphomas and other diseases. We are learning new things every day.

Q: You've written that hematopathologists often serve as consultants to clinicians, patients, and other pathologists. How does educating patients and clinicians fit into your life?
JAFFE: First, let me say that one of my pet peeves is that pathologists are often misunderstood in the press. Pathologists are regarded as Dr. Death locked in the morgue. The average citizen thinks that we only do autopsies and are not really involved in a clinical situation. But in order to give the right treatment, one must have the right diagnosis, and the pathologist is critical to coming up with the right diagnosis. Pathologists can also serve as consultants to patients.

I receive a lot of cases and consultations from the outside. Patients often call me to discuss their diagnosis, the implications of their diagnosis, and what course of therapy they might choose. In a way, they regard me as a neutral consultant because I don't have a stake in how they are going to be treated. I think the average citizen doesn't realize that pathologists can play that role, and should play that role.

Q: What types of physicians typically seek confirmatory diagnoses? How many requests do you receive and from where?
JAFFE: I receive approximately 1,700 cases in consultation a year—about 35 a week—the majority from within the United States, but about 5 to 10 percent from other countries. In the past few months, we have received consultations from South Africa, Brazil, Argentina, England, Australia, New Zealand, Sweden, Norway, Italy, Spain, Japan, and Korea.

The cases come from both university centers and community practices. Either the pathologist who originally saw the case or the clinician taking care of the patient may seek the consultation. Sometimes pathologists on the outside have provided different diagnoses, and the physicians are trying to resolve a discrepancy.

Q: Are the samples you receive in slide form only, or do you also receive tissue samples, X-rays, ELISA data, or other diagnostic indicators?
JAFFE: A consultation case may contain anywhere from one or two slides to 50 or more slides in some complicated cases. For example, in a difficult case in which a precise diagnosis is elusive, we may receive multiple biopsies performed over a period of months to years. In nearly all cases, we receive the tissue embedded in paraffin (paraffin blocks) in addition to glass slides. The paraffin blocks are used for immunohistochemical studies, in situ hybridization, or PCR analysis of relevant DNA sequences. In some instances, we may receive either snap-frozen tissue samples or even unfixed tissue in media for more elaborate studies. The X-rays (CT scans, conventional X-rays) are sent in a small proportion of cases, but we always insist on receiving an adequate clinical history, so that we may evaluate the pathology in the clinical context.

Q: How do you proceed once samples have arrived? Do you consult with other NIH colleagues? Do you keep the samples? Do you respond formally or informally?
JAFFE: We utilize the expertise of other colleagues in evaluating the pathologic findings. We rely heavily on the ancillary laboratory services of immunohistochemistry and molecular diagnostics provided by Mark Raffeld and Lynn Sorbara of the Laboratory of Pathology (NCI). If we have viable cells, we may call upon Maryalice Stetler-Stevenson to perform flow cytometry, or cells may be provided to Diane Arthur for cytogenetic studies. Once the diagnosis is established, the patient may be referred to our clinical colleagues for admission to NIH protocols or advice about treatment alternatives. We refer many cases to Wyndham Wilson of the NCI Medicine Branch. Cases with a differential diagnosis of autoimmune lymphoproliferative syndrome will be referred to Stephen Straus (NIAID; now director of the National Center for Complementary and Alternative Medicine [NCCAM]).

We always retain representative routine slides for our files, and any immunohistochemical stains performed in our laboratory are retained in our archives. It is relatively common for us to receive additional biopsies on the same patient later, and it is important for us to be able to refer back to prior material.

We always issue a formal pathology report, which is sent to the submitting physician, and in some cases to other pathologists or clinicians involved in the patient's care. In cases of clinical urgency, we provide an immediate verbal diagnosis over the phone.

Q: Do typical problems or inquiries regularly present themselves, or do you more often see unique cases?
JAFFE: Both. There are some regularly occurring diagnostic problems that we see often, such as the differential diagnosis between follicular lymphoma and follicular hyperplasia, or whether a biopsy is diagnostic of Hodgkin's disease. However—especially for cases sent from other academic institutions—we often receive a case because the topic is one on which we've published or have a research interest. Some unique cases may lead to descriptions of new entities.

Q: Can you give us a few examples?
JAFFE: More than 10 years ago we received a number of cases that were thought to be panniculitis, or an inflammation of the subcutaneous adipose tissues. Our studies of these cases led us to conclude that this was a unique form of T-cell lymphoma, subsequently termed "subcutaneous panniculitis-like T-cell lymphoma." This rare form of lymphoma was frequently associated with a secondary syndrome in which the histiocytes (macrophages) of the patient were stimulated to undergo phagocytosis. The patients developed a fulminant hemophagocytic syndrome that was fatal in most cases.

After our publications appeared, this form of lymphoma was recognized as a distinct entity in the REAL classification and the WHO scheme. We pursued laboratory studies to try to understand the pathogenesis of the hemophagocytic syndrome that supervenes in these patients and uncovered increased expression of certain cytokines and chemokines in these tissues. More accurate diagnosis of this disease in its early stages has led to earlier and more effective therapy, improving on the clinical outlook for the patients.

Our studies have also led to new clinical protocols at NIH. For example, some years ago we were interested in trying

to understand a rare type of pulmonary lymphoma, termed lymphomatoid granulomatosis. We showed that the Epstein-Barr virus played a critical role in this type of lymphoma and that many patients had underlying immune deficiencies. Through collaborations with Wyndham Wilson, new clinical protocols were developed. Wilson has shown that interferon-α can be very effective in managing many of these patients, and that they may not require aggressive chemotherapy.

Sometimes the rewards are very immediate and personal, such as making a diagnosis of Kikuchi's disease, a benign self-limited condition, in a young woman who was about to begin chemotherapy for what was thought to be an aggressive type of lymphoma. It is especially gratifying to be able to provide such good news to a patient.

Q: Could you identify a career landmark or particular publication that catalyzed your expert status and initiated these consultations?

JAFFE: I think one's reputation as a consultant is built gradually over many years. I enjoy teaching and lecture frequently at national and international meetings and at medical schools. In 1984, I wrote and edited a textbook on the interpretation of lymph node biopsies that became very popular.

Consultations often come about because of publications in specialized areas. Our studies showed that Hodgkin's disease often occurred in patients with B-cell lymphoma, either in the same lymph node—so-called composite lymphoma—or sequentially with B-cell lymphomas. Because of our publications in this area, we received additional cases in consultation, enabling us to further understand this phenomenon. More recent studies from several laboratories have proven that the malignant cell of Hodgkin's disease is B-cell in nearly all cases, in particular, a B-cell derived from the lymphoid follicle. Follicular lymphoma was the most common of lymphomas we saw in association with Hodgkin's disease.

Q: What do you find most intriguing or challenging about your role as a worldwide advisor? Do you enjoy it?

JAFFE: In sitting down at the microscope everyday, I feel a bit like Hercule Poirot trying to solve a murder mystery. I always know I will see something challenging and interesting and that will pique my interest to try to understand it further. Diagnostic pathology is a window on the structure-function relationship of the human body. It is also fun!

About a week ago, we received a lymph node from a patient in San Francisco with a peculiar histiocytic reaction. The submitting pathologist was very perplexed by this process. Could it be some bizarre infection? I recognized it as a special type of reaction seen in patients who have received hip prostheses, and it is caused by a reaction to titanium and cobalt-chromium found in prosthetic devices. I called the pathologist to tell him that his patient, a 78-year-old female, must have had her hip replaced. He checked the medical record, and indeed, the patient had received a hip replacement six months earlier. I felt a like a psychic, and, of course, the pathologist also was delighted to have his mystery solved. ■

JSPS Fellowships

May 19 is the deadline for the next round of JSPS fellowships, sponsored by the Japan Society for the Promotion of Science, in cooperation with the Fogarty International Center (FIC) and OIR.

Twenty fellowships will be awarded to support the research in NIH laboratories of young Japanese postdoctoral researchers who intend to have research positions at Japanese universities or other academic institutions in Japan. The fellowship lasts for up to two years and must begin on January 1, February 1, or March 1, 2001.

Candidates must be under 34 or 36 years old (depending on field) as of April 1, 2000, be Japanese citizens or permanent residents of Japan, and hold a doctoral degree.

Applications should be submitted to FIC in both Japanese and English. For application forms, and further information, contact Kathleen Michels, JSPS Programs, Division of International Training and Research, Fogarty International Center, NIH, Bethesda, MD 20892-2220; phone: (301) 496-1653; fax: (301) 402-0779; e-mail: **<jsps@nih.gov>**.

Fare Thee Well

The seventh annual Fellows Award for Research Excellence—FARE 2001—competition will again provide recognition for outstanding scientific research performed by intramural postdoctoral fellows. FARE winners will each receive a $1000 travel award to use for attending and presenting their work at a scientific meeting between October 1, 2000, and September 30, 2001.

The competition is open to postdoctoral IRTAs, visiting fellows, and other fellows with less than 5 years total postdoctoral experience in the NIH intramural research program. Pre-IRTAs performing their dissertation research at NIH are also eligible to compete. Visiting fellows and scientists must not have been tenured at their home institute. Questions about eligibility should be addressed to your institute's scientific director.

Fellows are asked to submit their application, including abstract, electronically from **May 1–May 31, 2000 (5:00 p.m., EST)**, via the NIH Fellows Committee web site: **<ftp://helix.nih.gov/felcom/index.html>**.

Those who cannot access the electronic application in their laboratory can find additional computers at the Scientific Computing Resource Center in Bldg. 12A, Rm 1018, the User Resource Center in Bldg. 31, Rm B2B47, as well as the NIH Library in Bldg. 10. Abstracts are evaluated anonymously on scientific merit, originality, experimental design, and overall quality and presentation. Winners will be announced by September 2000.

Questions about FARE 2001 may also be addressed to your institute's Fellows Committee representative or to **<FARE2001@nih.gov>**.

FARE 2001 is sponsored by the NIH Fellows Committee, Scientific Directors, NIH Office of Research on Women's Health, and NIH Office of Education. The FARE 2001 award is funded by the Scientific Directors and NIH Office of Research on Women's Health. ■

Senators Take a Look at Gene Therapy Oversight As RAC Keeps On Keeping On

by Fran Pollner

It was almost business as usual at the first meeting of the year of the NIH Recombinant DNA Advisory Committee (RAC), held here March 8–10; members of the press attended but in nowhere near the numbers that overwhelmed the preceding RAC meeting in December. That meeting, convened in the wake of the death of Jesse Gelsinger, had focused on gene therapy oversight, the safety of adenoviral vectors in general, and the conduct of the trial in which Gelsinger was a volunteer in particular (see "Gene Therapy Trial and Errors Raise Scientific, Ethical, and Oversight Questions," *The NIH Catalyst*, January-February 2000, page 1).

Fran Pollner

RAC Chair Claudia Mickelson

In the three-month interval between the two RAC meetings, the Food and Drug Administration suspended all clinical gene therapy trials sponsored by investigator James Wilson and the Institute for Human Gene Therapy at the University of Pennsylvania, where Gelsinger died; NIH and FDA have been revisiting their gene therapy oversight roles; a Senate panel held a hearing on the issue; and the RAC continued its daily business of scrutinizing novel gene therapy protocols and advising investigators on needed modifications.

On the Hill

At the Senate hearing before the Public Health Subcommittee, chaired by Bill Frist (R-Tenn.), lawmakers challenged FDA and NIH to improve gene therapy oversight procedures. The system, they said, is "failing." They were especially miffed by the failure of investigators to report adverse events to NIH and suggested that researchers may have misinterpreted the RAC's loss of protocol approval authority as license to ignore reporting regulations.

Paul Gelsinger, the father of Jesse, appeared with his lawyers and testified that he and his son had been misled, that his consent had been "informed" by documents and talks with the investigators that downplayed risks, omitted past adverse results, and implied unrealistic benefit. He called for the establishment of an independent body of knowledgeable persons who could serve as advisors in the informed consent process. Other witnesses and, later, Sen. Ted Kennedy (D-Mass.) called for the establishment of a national independent Data Safety and Monitoring Board for all gene therapy trials.

Missing from the Senate hearing were the investigators in the UPenn trial. Wilson and his colleagues had been invited to attend, according to a Senate staffer, but had declined, and Frist chose not to exercise his subpoena authority. Frist plans to hold additional hearings and followed up on the first one with written questions for FDA and NIH. Those directed to NIH focused on site visits to gene therapy grantees and financial conflicts of interest, progress in developing an interactive gene therapy database, the RAC's role, and adverse event reporting requirements.

At the RAC

The death of Jesse Gelsinger colored nearly every item on the RAC's packed three-day agenda—from the review of nine novel gene therapy protocols to discussions of adverse events reporting and the boundaries of RAC authority. The adverse events issue proved thorny, with RAC members in a "stalemate," in the words of RAC chair Claudia Mickelson, over which adverse events ought to be reported to the group and how quickly. Mickelson insisted agreement be reached by the RAC's June meeting.

Regarding RAC's authority, most members appeared satisfied with the value of their work and the influence it has on the field of gene therapy. Although there were a few comments on the need for "teeth"—in the form of protocol-approval authority—to ensure compliance with RAC requests for protocol changes or additional preclinical studies, there was general consensus that the FDA, investigators, institutional review boards (IRBs), legislators, and the public take the RAC's advice very seriously. Some members wanted more formal feedback procedures to learn whether their advice had actually been followed, and several emphasized the need for optimal timing of RAC protocol deliberations—namely, *before* approval by other bodies, such as an IRB or FDA.

RAC scientific and ethical expertise, as well as power of persuasion, was much in evidence during protocol reviews. The lead-off protocol actually served as a prototype for extended scrutiny of a new vector—the gutless (internally deleted) adenoviral vector—in this case carrying the gene for factor VIII. The FDA had requested the RAC review; both the principal investigator and the sponsor said they would not proceed with the trial without RAC approval. Indeed, two other unrelated protocols originally on the agenda had received such extensive preliminary comments from RAC reviewers that the sponsors had withdrawn their submissions before the meeting.

Most of the remaining protocols were Phase I studies involving cancer patients or patients with monogeneic deficiency conditions, such as hemophilia; several used adenoviral or adeno-associated vectors to deliver the transgene. In response to RAC requests, often informed by the lessons of the Gelsinger case, investigators variously agreed to institute arithmetic rather than half-log increments in the higher dosage ranges in their dose-escalation studies, to monitor cytokine levels and other immune parameters, and to do more preclinical studies on biodistribution of the vector. Attention was paid to explicit criteria for stopping a study to assess adverse effects, as well as to full disclosure of risks in informed consent documents.

Much of the discussion was in conformity with the recommendation of a RAC working group that clinical trials using adenoviral vectors "continue with caution" while vector standards and characterizations are further developed. The working group also endorsed the idea of having "patient advocates" to address conflicts of interest and to optimize informed decision making—similar to the proposal made earlier at the Senate hearing and repeated at the RAC meeting by Paul Gelsinger.

Fran Pollner

Jeremy Rifkin (left) confers with Paul Gelsinger (middle) and Gelsinger's attorney during a break in the RAC proceedings

The RAC rejected a proposal by Jeremy Rifkin, of the Washington-based Foundation for Economic Trends, to halt the use of all viral vectors in gene therapy protocols, except as a last-resort in life-threatening illness. ■

WHO Panel Recommends Resumption Of Rotavirus Vaccine Field Studies in Developing Countries

by Fran Pollner

The sands have once again shifted in the status of the world's first licensed rotavirus vaccine—and NIH's Al Kapikian, who headed the research culminating in the vaccine's approval, continues to explore avenues of rotavirus vaccine research.

An international assembly of vaccinologists, epidemiologists, and public health officers has recommended the resumption of field trials to determine the safety and efficacy in developing countries of the rotavirus vaccine whose approved use in the United States was suspended after the emergence postmarketing of vaccine-related cases of intussusception, or intestinal prolapse, a serious but poorly understood condition in which the intestine telescopes into itself. Treatment may require surgery, which can be problematic in developing countries.

Convened by the World Health Organization, the assembly met in Geneva in February to consider future rotavirus vaccine development in developing countries, with a special focus on the risks and benefits of RotaShield, the Wyeth-Ayerst product brought to the U.S. market in the summer of 1998 but withdrawn by the manufacturer last October. That action had ended activity the world over involving the only vaccine licensed for use against rotavirus.

"The basic ethical question the Geneva group had to address," said Kapikian, head of the Epidemiology Section in NIAID's Laboratory of Infectious Diseases, "was: 'Can a vaccine withdrawn from use in the United States be used in developing countries? Would this be dispensing second-class medicine to developing countries?'"

The group concluded it would be "immoral not to proceed" with the testing of RotaShield in developing nations, where rotaviral diarrhea kills almost 100 children under the age of 5 every hour.

"They agreed that inaction is not a morally neutral position" when the death toll is about 800,000 worldwide yearly, and researching another vaccine could take perhaps four to seven additional years—with no guarantee that safety and efficacy would exceed RotaShield's.

"The hurdle now," Kapikian added, "is the availability of the Wyeth-Ayerst vaccine," a subject he addressed in a letter to the company immediately upon his return from the Geneva meeting. At the time the company withdrew the vaccine, it had supplied only the U.S. market and had not begun distributing the product to the 15 Western European nations that had also registered it for use or to any developing nations. Representatives of the company were at the Geneva proceedings—but not the ultimate "decision-makers," he said.

Fran Pollner

Al Kapikian

RotaShield's future had been in limbo since last July when the Food and Drug Administration (FDA) advised physicians to suspend its use until the emerging risk of vaccine-related intussusception was clarified. A few months later, in October, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention withdrew its recommendation that babies be vaccinated against rotavirus at 2, 4, and 6 months. The manufacturer then withdrew the product.

The vaccine had been endorsed by ACIP and approved by FDA in the summer of 1998, the capstone of a quarter-century of basic and clinical research with a strain of rhesus rotavirus that produced a quadrivalent, live-virus oral vaccine. The vaccine had proved safe and efficacious in preventing severe rotaviral-related diarrhea in clinical trials involving more than 7,000 children. The research program was carried out under Kapikian's direction (see "More than Two Decades of Research Culminates in Rotavirus Vaccine," page 9, *The NIH Catalyst*, March–April 1999).

But within a year of the vaccine's marketing, there appeared a report in the July 16, 1999, *MMWR* (*Morbidity and Mortality Weekly Report*) of 15 cases of intussusception among vaccinated infants. Thirteen of the 15 occurred after the first dose; in 12 of 15, onset occurred within one week of any dose. The cases had been reported to the joint CDC-FDA Vaccine Adverse Events Reporting System. Further investigation of this phenomenon uncovered 102 confirmed or presumptive cases of intussusception following the administration of about one and a half million vaccine doses.

"We need to understand just what happened here. It was such a surprise to everybody," Kapikian said in an earlier interview with the *Catalyst* late last year, after he'd detailed the chain of events for the NIH community at a Kinyoun lecture here. An increased intussusception rate had not been observed in any of the clinical trials that led to FDA approval, raising the question of just how many infants need to be included in the testing of this and any other rotavirus vaccine before an increased rate of a rare event like intussusception emerges.

Based on New York State's 1991–1997 hospitalization rate for intussusception of 51/100,000 infants during the first year of life, the expected yearly background intussusception rate would be about 500 per million in the unvaccinated population over a one-year period. Although reviews of the outcomes among various cohorts of vaccinated babies reveal rates that appear to be lower than that, the time periods covered have not been comparable, Kapikian noted. Also unclear are whether wild-type rotavirus infection increases intussusception risk and whether an effective rotavirus vaccine would, therefore, decrease the overall rate in the long-term. "That clustering in the first week after the first dose is significant, but we really don't know what happens over a year's time," Kapikian observed. "Is there a compensatory decrease after that first week?"

Once the rate of infant intussusception attributable to rotavirus vaccine is established, the risk-benefit ratio among different populations of infants may be assessed and public health decisions made. Suspended WHO studies planned in Asia and Africa to address these issues can now resume, contingent on the availability of the vaccine itself.

Kapikian's team has been collaborating with researchers in Finland and at Johns Hopkins University in Baltimore in studies of a "second-generation" rotavirus vaccine based on a bovine strain, which is less likely to induce fevers in the week after vaccination. He and his team had developed a six-antigen construct before the hiatus.

Clinical Research Standards
continued from page 1

they were revised accordingly and finally approved by the institute directors. In December 1999, the MEC issued the *Standards for Clinical Research at NIH.* From retreat to delivery took nine months and "no less pain" than that other nine-month event, Gallin observes.

Gallin and Michael Gottesman, deputy director for intramural research, are developing a process for the implementation of the standards and review of institute compliance, which will be the subject of a future *Catalyst* article. Implementation of the data management standards, in particular, will be aided by the Clinical Research Information System (CRIS), which the CC is building to replace the current Medical Information System and which will contain fully "searchable and minable" clinical care data for all patients enrolled in CC trials. It will also "interface in a seamless way" with the laboratory data kept by investigators at each institute.

"This will be a challenge, but we'll meet it," Gallin says. The $42–50 million CRIS project will be implemented gradually over a four- to- five-year period and will also be addressed in a future *Catalyst* article. The standards for clinical research are reprinted below.

—F.P.

Clinical Research Standards

Introduction

Adequate training and the infrastructure to support principal investigators conducting clinical research are essential to patient safety, protocol implementation, and quality assurance, especially in interventional clinical trials. Indeed, even in natural history studies, such infrastructure can only enhance quality and access to the research by ensuring that data are collected as required by the protocol and are stored in a way that allows access to the information without dependence on any individual clinical researcher.

The International Conference on Harmonisation, a consortium of regulatory bodies for the European Union, Japan, and the United States (Food and Drug Administration), has issued a series of guidelines for good clinical research that has begun to define the resources required for clinical principal investigators (PIs). A central requirement identified by the Conference is the availability of "an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely." (1)

To assure patient safety and high quality NIH intramural clinical research programs, the Medical Executive Committee of the NIH Clinical Center has developed the following essential standards for performing clinical research categorized in six subject areas:

1. Clinical Informatics, Data Management, and Protocol Tracking
2. Biostatistics Support
3. Quality Assurance and Quality Control
4. Protocol Review
5. Human Resources and Physical Plant
6. Training and Education

Each standard, with its rationale, is listed below:

1. Clinical Informatics, Data Management, and Protocol Tracking

Rationale

Collecting clinical data is a complex task that must be integrated into the medical practices of the institution. To monitor the study's progress and patient safety, data collection is best done as data are generated. Data management organized and supported at the institute level is more efficient and reliable than that left to the individual investigator. There are often unforeseen uses for the kinds of information gathered in the conduct of a clinical trial, and a central database, with appropriate archiving, assures that this information remains the legacy of the institute.

Standard

Each institute sponsoring clinical research should develop a central clinical investigations database that maintains all data specified to be collected in the clinical study (either intervention or natural history). The clinical research information system being developed by the Clinical Center will interface with and support each institute's clinical research needs. Data management infrastructure is required by institutes to maintain their central data registry, to enhance existing databases, to provide eligibility checklists, to record patient randomization and entry into their protocols, to provide report generation, data warehousing and data entry forms, and to monitor data collection.

2. Biostatistics Support

Rationale

The design of clinical trials should be based on sound statistical principles. Issues such as sample size, stopping rules, endpoints, and the feasibility of relating endpoints to objectives are pivotal to a successful trial. Typically, if the PI is not a skilled biostatistician, a biostatistician should be listed as an associate investigator on the protocol and should be involved in the protocol at all stages from design to analysis of results.

Standard

All clinical protocols must be reviewed by a qualified biostatistician prior to approval and implementation.

3. Quality Assurance and Quality Control

Rationale

The International Conference on Harmonisation is very clear on the responsibilities of research sponsors. The sponsor is defined as the organization that "takes responsibility for the initiation, management and financing of a clinical trial." In the context of the intramural program, the research sponsor is each institute conducting intramural clinical research.

The sponsor "is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures to ensure that trials are conducted and data generated, documented, and reported in compliance with the protocol, good clinical practices, and the applicable regulatory requirements." To accomplish this, quality assurance programs are necessary to assure that each participating investigator is fulfilling his/her responsibilities. Quality assurance provides institutes with data about the quality of execution of their clinical research, and it provides investigators an

(1) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Guidance for Industry: E6, Good Clinical Practice, Consolidated Guideline, April 1996, Section 4—Investigator:
<http://www.fda.gov/cder/guidance/959fnl.pdf>.

opportunity to learn through external evaluation.

Some interventional trials should be overseen by an external expert committee (data safety and monitoring board [DSMB]) to assure that adverse events are recognized and reported and that protocols are implemented in conformance to the protocol design and are closed to accrual when endpoints are met or unanticipated adverse events occur. At a minimum, all randomized or blinded studies should be reviewed at least semiannually by a DSMB.

Standard

Each institute must establish a quality assurance program with infrastructure that ensures that clinical trials are monitored adequately and centrally. The institute should determine the appropriate extent and nature of monitoring. This determination should be based on considerations of the study objectives, purpose, design, complexity, blinding, size, and endpoints and should include the following:

- Onsite protocol monitoring during clinical trials. Statistically controlled sampling is an acceptable method for selecting the data to be verified. For interventional trials, the institutes should demonstrate a capacity to review a minimum of 10 percent of patient records on selected clinical trials to assure data accuracy, protocol compliance, and adherence to regulatory requirements.
- Establishment of an independent DSMB for at least a semiannual overview of all randomized blinded studies.

4. Protocol Review

Rationale

All protocols involving human subjects must undergo review of scientific content by an institute scientific review committee. These protocol review committees assess scientific quality, the importance to clinical practice, and the appropriateness of the study to the sponsoring institute. Following the scientific review, all protocols must be reviewed by an institutional review board (IRB) to establish and ensure patient safety and good ethical conduct of the study.

Standard

Each institute must provide or have access to:

- Scientific review by a protocol review committee.
- Infrastructure (for example, administrative staff) to support an appropriately constituted IRB.

5. Human Resources and Physical Plant

Rationale

A cadre of skilled personnel is required for support and oversight of clinical trials. The appropriate organization of a clinical trial team may differ depending on program objectives. PIs need to be supported by a team comprised of an appropriate mix of case managers, research nurses, physician assistants, nurse practitioners, data managers, and programmers.

Standard

Necessary personnel, office space proximal to patient care areas, and accompanying resources are required to support the clinical research infrastructure.

6. Training and Education

Rationale

Clinical protocol design requires a working knowledge of clinical trials methodology, biostatistics, and regulatory medicine. Similarly, monitoring the trial during its execution involves many distinct responsibilities, including reviewing each case record to confirm protocol eligibility, reviewing each case record to determine compliance with the protocol, reporting adverse events to the IRB, determining necessary changes in the protocol and the informed consent documents and submitting them as protocol amendments to the IRB, monitoring accrual to the study, and stopping the study when the requirements of the study design have been fulfilled or when it is clear that the rate of accrual fails to meet expectations.

Training and education are first-order requirements to ensure that the PIs on clinical trials have a consistent and complete understanding of their responsibilities.

Standard

- All clinical PIs are required to take an overview training course, or equivalent, on the roles and responsibilities of clinical investigators. This course will be developed by the Clinical Center.
- All IRB chairs and IRB members (including lay members) will receive orientation materials and are required to take specialized training modules provided by the Clinical Center.

—The Medical Executive Committee
NIH Clinical Center
December 1999

Spring Training

The NIH Training Center, run by the Office of Human Resource Development, has numerous course offerings throughout the year. The courses are available through the NIH Integrated Training System (NIHITS), an electronic process whereby the sponsoring institute nominates and covers the course fee for the nominated individual. Following are a few examples of courses scheduled for April and May, some of which are repeated at later dates.

April 25–26 or July 18–19, 9–4, Executive Plaza South, Room 9: **How To Manage Conflict: Solving Problems at Work** (1456). **Nomination deadline March 28 or June 20**.

April 27–28 or June 8–9, 9–4, Executive Plaza South, Room 8: **Scientific and Technical Briefing** (2160). **Nomination deadline March 31 or May 11.**.

May 2–3 orSeptember 20–21, 9–4, Executive Plaza South, Room 8, **Scientific and Technical Editing** (1506). **Nomination deadline April 4 or August 23.**

May 9–11 or September 19–21, 9–4, Executive Plaza South, Room 8: **Scientific and Technical Writing** (2154). **Nomination deadline April 11 or August 22.**.

For more detailed course information, as well as the complete course offerings, call HRDD at 301-496-621, or visit the HRDD web site at

<http://trainingcenter.od.nih.gov>.

Worksite Lactation

Women working at NIH who have registered for the Worksite Lactation Program can also take two classes this spring related to breast-feeding. To register for the lactation program, visit **<http://odp.od.nih.gov/whpp/events/lactation.html>.**

For more information, contact Jane Balkam at 301-435-7850 or e-mail at **<balkamj@od.nih.gov>.**

People

Recently Tenured

Andres Buonanno *received his Ph.D. in 1987 from Washington University Medical School in St. Louis, where he worked under the mentorship of the late John Merlie. He joined the NICHD Laboratory of Developmental Neurobiology in 1988 and is now a senior investigator heading the Section on Molecular Neurobiology.*

A fundamental objective in neurobiology is to understand how connections in the nervous system are remodeled during development and by experience. Although we have known for more than two decades that electrical currents elicited by neurons have profound effects on the expression of receptors, channels, and other structural proteins, little is known of the molecular pathways that couple neural depolarization to specific changes in gene expression.

Fran Pollner

Andres Buonanno

There is increasing evidence that calcium influx is an important constituent of activity-dependent regulation. But there are more questions than answers in resolving how calcium is coupled to changes in gene transcription. How are different frequencies or patterns of action potentials sensed, and then decoded, to selectively repress or stimulate transcription? Which signal transduction pathways and transcription factors are involved?

To identify the molecular pathways that mediate activity-transcription coupling in excitable tissues, my laboratory has used two experimental systems: In the brain, we have studied the activity-dependent regulation of glutamate neurotransmitter receptors; and in muscle, we have analyzed genes that are differentially regulated by specific patterns of depolarization.

The opening of an NMDA receptor by its neurotransmitter, glutamate, results in synaptic calcium currents, activation of signal transduction pathways, and a prolonged strengthening of synaptic transmission. This activity-dependent process, known as long-term potentiation, underlies complex behaviors such as learning and memory and the wiring of the nervous system. Interestingly, NMDA receptors are not only necessary to mediate these activity-dependent changes in the brain but, as we found, the subunit composition of the receptor is regulated by neural activity.

The signaling properties of NMDA receptors, which comprise a common NR1 and distinct NR2 subunits (NR2A-D), depend on the heteromeric composition of the receptor. The most striking change in the composition of the receptor occurs in the developing cerebellar granule neurons, where the expression of the NR2B subunit is shut off and replaced by expression of the NR2C subunits. We initially observed that this subunit switch, which has profound effects on the functional properties of the receptor, coincides with the innervation of granule neurons by incoming mossy fiber inputs during the first weeks of postnatal development.

We then tested the hypothesis that the innervation of granule neurons, and their depolarization by the glutamatergic mossy fiber inputs, is responsible for the NR2 subunit switch. Using transgenic mice and transfected granule neurons, we identified DNA regulatory sequences that confer neural specificity and repress the NR2B gene in response to neural activity. We then demonstrated that the upregulation of the NR2C gene requires signaling via two converging pathways: the activation of NMDA and ErbB receptors. The ErbBs are tyrosine kinase receptors that bind the neurotrophic factor neuregulin, which is found together with glutamate at the mossy fiber synapses. This was the first demonstration of factors regulating NMDA receptors and a functional role of neuregulin in neurons.

Consistent with the developmental requirement for NMDA and ErbB receptor co-signaling, we recently demonstrated that these receptors are co-localized at a structure known as the postsynaptic density (PSD). The PSD is a dense plaque rich in neurotransmitter receptors and channels adjacent to the presynaptic terminal that serves to couple trans-synaptic signaling. Using the yeast-2-hybrid system and biochemical assays, we demonstrated that the carboxyl end of the ErbB receptor interacts with the same PDZ domain-containing proteins that associate with NMDA receptors at PSDs. Proteins harboring PDZ domains, a motif necessary for protein-protein interactions, may act as "transductosomes" because they physically link membrane neurotransmitter receptors to signal-transducing enzymes in the cell.

A major emphasis of our future studies will be to analyze how activity coupled to neuregulin signaling regulates NR2 expression in other regions of the brain. Experiments are in progress to identify the factors that couple signaling via these pathways to transcription of NMDA receptor genes.

Another goal of our research is to understand how neural activity and specific depolarization frequencies regulate muscle function. The properties of slow (red) and fast (white) skeletal muscles are determined by the differential transcription of genes encoding contractile proteins. These genes are regulated by the slow or fast frequencies of motor neuron action potentials used to depolarize muscles.

We analyzed the expression of two contractile proteins known as troponins (Tn) that are selectively expressed in either slow- or fast-twitch muscles. Initially we demonstrated that Tn slow and fast expression is reversibly switched by simply changing the frequencies used to artificially depolarize denervated rat muscles. Interestingly, we found that activity can elicit opposing effects on the transcription of different genes. Transcription of Tn genes is stimulated by specific frequencies of depolarization, whereas expression of the "master regulatory factors"—MyoD and myogenin—is repressed by electrical activity, irrespective of frequency.

To isolate the factors that regulate the Tn genes, we began by identifying the regulatory sequences that confer specificity. Because fiber types do not develop in vitro, we used transgenic mice to identify the first enhancers known to confer either slow or fast fiber-type specificity in muscle. Surprisingly, we found that the Tn SURE (slow upstream regulatory element) and FIRE (fast intronic regulatory element) harbored four homologous DNA elements essential for activity and differed in a novel fifth element. By cutting SURE or FIRE in half and expressing the deletions in mice, we found that the downstream halves directed expression in all types of skeletal muscles (not other types of tissues), whereas the upstream regions harboring the novel element were necessary to confer slow or fast muscle specificity. The DNA element is now being used in a yeast-1-hybrid system to clone cDNAs that may encode the regulatory factors that are modulated by neural impulses and that regulate muscle fiber-type specificity.

Using these experimental approaches, we hope to understand the intriguing regulatory puzzle of how specific patterns of neural activity are sensed, and then decoded, to modify the properties of neurons and muscles in response to experience.

Mark Mattson *received his Ph.D. in biology from the University of Iowa in Iowa City in 1986. After postdoctoral work at Colorado State University in Fort Collins, he took a faculty position at the Sanders-Brown Research Center on Aging at the University of Kentucky in Lexington, where he advanced to full professor in 1997. He joined NIH in 2000 as chief of the Laboratory of Neurosciences at the NIA Gerontology Research Center in Baltimore.*

Mark Mattson

The long-term goal of research in my laboratory is to elucidate the molecular and cellular mechanisms responsible for nerve cell dysfunction and degeneration in age-related disorders such as Alzheimer's and Parkinson's diseases. Complementary studies are aimed at identifying environmental and genetic factors that allow individuals to age successfully with little or no brain dysfunction. Our work uses a battery of cell culture and animal models of neurodegenerative disorders, in combination with analyses of brain tissue from patients with the disorders.

Over the past 12 years, we have published findings on:

- the function of the β-amyloid precursor protein,
- the neurotoxic mechanism of amyloid β-peptide,
- mutations in presenilins and how they promote age-related synaptic dysfunction and neuronal degeneration,
- the signal transduction mechanisms of neurotrophic factors and cytokines that may increase or decrease neuronal resistance to age-related disease,
- the mechanisms whereby dietary restriction (which extends lifespan) benefits the aging brain.

Ongoing projects include experiments to delineate the molecular events that occur locally in synaptic terminals that mediate synaptic dysfunction and degeneration in neurodegenerative disorders. For example, we have found that biochemical cascades that mediate apoptosis can be activated in pre- and postsynaptic terminals. At these locations, apoptotic cascades can modify various synaptic regulatory systems, including glutamate receptor channels, cytoskeletal components, and mitochondrial function.

We have also identified signaling pathways that can stabilize synaptic metabolism and ion homeostasis. For example, neurotrophic factors—such as brain-derived growth factor, basic fibroblast growth factor, and activity-dependent neurotrophic factor—can enhance synaptic glucose transport and mitochondrial function; and signaling via integrins (membrane receptors activated by specific extracellular matrix proteins) through a pathway involving Akt kinase can protect neurons against synaptically driven cell death. In order to elucidate roles for injury- and stress-responsive signaling pathways in neurological disorders, we have used gene-targeting approaches to generate mice that lack specific signaling proteins. For example, we have found that mice lacking p55 tumor necrosis factor receptor are more vulnerable to excitotoxic and ischemic brain injury than are wild-type mice; mice lacking the p50 subunit of the transcription factor NF-κB are also more vulnerable to excitotoxic injury; and mice lacking acidic sphingomyelinase exhibit a reduced cytokine response, decreased brain injury, and improved behavioral outcome in a focal cerebral ischemia stroke model.

Telomerase is a reverse transcriptase that adds a six-base DNA repeat onto the ends of chromosomes and thereby prevents their shortening. Telomerase is linked to cell immortalization and has been touted as an anti-aging enzyme. We have found that TERT, the catalytic subunit of telomerase, is widely expressed in neurons throughout the rodent brain during embryonic and early postnatal development but is absent from neurons in the adult brain.

When we suppressed telomerase expression or function using genetic and pharmacological approaches, we found that cultured embryonic brain neurons were more vulnerable to apoptosis induced by trophic factor withdrawal and insults (such as amyloid β-peptide, glutamate, and iron) relevant to the pathogenesis of Alzheimer's disease and other age-related neurodegenerative disorders. We are now in the process of generating transgenic mice that express TERT in neurons in the adult brain, with the goal of determining whether TERT will help protect neurons in animal models of neurodegenerative disorders.

Our recent findings suggest that TERT may suppress neuronal apoptosis, in part by inhibiting activity of the pro-apoptotic protein p53. In collaboration with Nigel Greig (Laboratory of Neurosciences), we have found that a chemical inhibitor of p53 is effective in protecting neurons against damage and death in experimental models of neurodegenerative disorders. We are also working to identify environmental signals, such as trophic factors and hormones that may ward off age-related neuronal degeneration.

We have recently gained insight into the mechanism whereby dietary restriction may benefit neurons in the aging brain. We found that levels of "stress proteins," including heat-shock protein-70 and glucose-regulated protein-78, as well as brain-derived neurotrophic factor and nerve growth factor, are increased in neurons in several different brain regions of mice and rats maintained on a dietary restriction regimen.

In collaboration with Don Ingram and Mark Lane (Laboratory of Neurosciences), who have shown that dietary restriction retards age-related changes in monkeys, we aim to establish whether similar molecular events occur in the brains of monkeys on a dietary restriction regimen. Based on our findings, we hope to develop strategies for preventing and treating neurodegenerative disorders of aging. ■

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The Work and Family Life Center Resource and Referral Services provides NIH employees with reliable and timely referrals* to many types of childcare, eldercare, and adult dependent care, **nationwide**. Call (301) 435-1619 for confidential information on:

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Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: clinical research standards for the IRP, gene therapy oversight, "plain language" plans, and your own research.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 1, Room 209.

In Future Issues...

- Science in Space: Astrobiology . . .
- . . . & Cyberspace and the IRP
- About FAES

1) What's your opinion of the new standards for carrying out clinical research at NIH?

2) Do you think there's a need for additional federal oversight of human gene therapy experiments? Should the NIH Recombinant DNA Advisory Committee (RAC) once again have protocol-approving authority, along with the Food and Drug Administration, for gene therapy clinical trials?

3) Do you see how your own writings could benefit from following the guidelines for "plain language" presented on pages 4 and 5 of this issue?

4) Is there some fascinating research going on in your laboratory you'd like the wider NIH community to know about?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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